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PRIMARY CANCER OF THE LUNG WITH SPECIAL CONSIDERATION OF ITS ETIOLOGY*

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I APPRECIATE very much the high honor which you have accorded me in inviting me to give this fifth James Ewing Memorial Lecture. Many years ago when Dr. Ewing first published his "Neoplastic Diseases" I was greatly stimulated by it. I wish sincerely that he was still alive to help solve some of the pathological problems concerned with the subject about which I am going to speak to you tonight.

Bronchiogenic carcinoma differs from other cancers in two important respects, 1) it has shown an enormous increase in the last thirty-five years and 2) there has been a progressively larger incidence in the male sex.

There can no longer be any reasonable doubt that the very great increase in the incidence of bronchiogenic carcinoma is real and not merely apparent. Kennaway and Kennaway,[1] in a study of death certi-

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ficates in England and Wales, found evidence of a great increase from 1928 to 1945, and more recently Doll and Hill[2] quote a British government report which shows that for the twenty-five year period from 1922 to 1947 the incidence of the condition found in autopsies in England and Wales increased fifteen times over what it had been previously. Actual figures on the increased incidence in the United States during the same period are not available but it is noteworthy that although Adler[3] in 1912 could collect only 374 cases from the world's literature, individual experiences in this country greatly exceed that total of reported cases from the whole world. For example, at the Barnes Hospital we have had 1375 proven cases in the last thirty years, or nearly four times as many as Adler could collect from the world's literature. In the United States statistical studies at the Charity Hospital of New Orleans by Ochsner and DeBakey,[4] at the St. Louis City Hospital by Wheeler[5] and at the Hines Veterans Hospital by Ariel, Avery, et al.[6] have all shown that in recent years bronchiogenic carcinoma has become the most frequent visceral cancer of the male patient. Cancer of the stomach which formerly occupied first place has been relegated, at least in those institutions, to second place.

No one can deny that there were excellent pathologists in the last century who certainly knew cancer when they saw it. It seems hardly likely that those of the caliber of Virchow, Cohnheim and Rokitansky could have missed recognizing the condition at autopsy as frequently as would have been necessary to account for the pronounced difference in incidence then as compared with now. Moreover, the argument advanced by some that the increase is only apparent because more people are reaching the cancer age now loses value when one realizes that not only is the number of cases increasing but, more striking, this cancer has changed its relative position in frequency. The fact that more people are now reaching the cancer age would not explain how it has happened that bronchiogenic carcinoma has advanced to a position of first place in men from one of about eighth place in frequency—and this all within the last thirty-five or forty years.

Along with the increased incidence of the condition there has also been a progressive distribution in favor of the male sex. For example, when Adler compiled his statistics the ratio of males to females was about three to one. In contrast, in our last 150 cases the ratio was 18.5 males to one female. In 100 consecutive cases collected by Lindskog[7]

between 1938 and 1943 he found the ratio 4.5 to 1 but in another series in 1947 and 1948 it had become twenty-four to one.

The preponderance of incidence in males raises the question of whether sexual factors play a role in conferring a relative immunity upon the female sex. In other words, does the state of femininity make it less possible to develop a bronchiogenic carcinoma?

To gain information on this question Kemler and the writer[8] used Greene's[9] method of transplantation of small fragments of human bronchiogenic carcinoma from a male subject into the anterior chamber of guinea pigs' eyes. Our experiments showed that the transplantation was equally successful in both female and male animals. Likewise Gumbreck[10] in assaying the male sex hormones in ten cases of bronchiogenic carcinoma in men found that there was no essential difference between the cancer subjects and normal controls of the same ages. Therefore it seems that the state of masculinity or femininity has no inherent quality that is responsible for the marked preponderance of incidence of bronchiogenic carcinoma in men.

From all of this it seems reasonable to assume that there has been something in our culture or methods of living in the last thirty or forty years which has been responsible for the remarkable increase of this cancer and that men have been more exposed to this carcinogenic influence than women. Occupational factors would seem to be relatively unimportant since all economic classes and men engaged in all kinds of occupations seem to be affected. The butcher, the baker and candlestick maker all are prone to have the condition. Moreover both urban and rural dwellers seem to be subject to it about equally.

When one speculates on what factors we are exposed to now different from those in existence formerly, various possibilities suggest themselves. One of these of course is the great increase in the use of petroleum products since this is the automobile age. Preliminary observations on this point, however, fail to show that oil field workers, garage mechanics and others particularly exposed to petroleum products or to inhalation of exhaust fumes from automobiles have a significantly greater incidence of the disease than others. Without mentioning other possibilities for which there is no striking incriminating evidence at the present time we can take up for consideration immediately one factor which seems to be very important. That factor is tobacco smoking, especially the use of cigarettes.

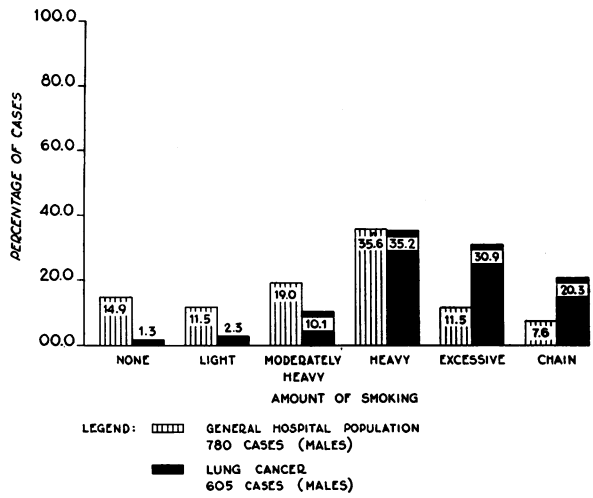

Fig. 1—In this chart a comparison is made between the amount of smoking done by 605 male patients with bronchiogenic carcinoma and 780 men without lung cancer of approximately the same age groups, economic status and percentage of urban and rural residence. "Light" smokers have used from 1 to 9 cigarettes per day for more than 20 years. "Moderately heavy" indicates 10 to 15 cigarettes per day for more than 20 years. "Heavy" smokers are those who have used from 16 to 20 cigarettes per day for more than 20 years. By "excessive" is indicated the use of from 21 to 34 cigarettes per day for 20 years, and by "chain" smokers is meant those who have used 35 cigarettes or more per day for at least 20 years

The idea that smoking may be an important factor in the etiology of bronchiogenic carcinoma has been suggested by many writers. Adler made such a suggestion in his monogragh. Tylecote,[11] Hoffman,[12] McNally,[13] Lickint,[14] Arkin and Wagner,[15] Roffo[16] and Müller[17] were additional workers who prior to 1940 thought that smoking, especially of cigarettes, was important in this respect. In 1941 Ochsner and DeBakey[18] called attention to the similarity of the curve of increased sales of cigarettes in this country to the greater prevalence of primary cancer of the lung.

Recently Wynder and the writer[19] made the largest statistical study of this question reported up to that time. A survey of the smoking habits was made in 684 proven cases of bronchiogenic carcinoma. The information was obtained by means of a personal interview with each patient.

A standard questionnaire was used and most of the interviews were made by two non-medical women who were ignorant of the diagnosis at the time they questioned the patients. The subjects of the interviews were from all social and economic classes and from widely scattered parts of the country. It was found that of 605 males with bronchiogenic carcinoma, other than adenocarcinoma, 96.5 per cent had smoked more than a half pack of cigarettes daily for more than twenty years as compared with 73.7 per cent of 780 males without lung cancer who had smoked as much and who were of a comparable age group. Even more impressive was the fact that among the lung cancer group 51.2 per cent had smoked more than a pack a day for at least twenty years as compared with only 19.1 per cent who had smoked that much in the group without lung cancer. In only 2 per cent of these cases did the patient not smoke at all or less than one-half pack of cigarettes daily. The most striking features revealed from the study were that in the correlation which seems to exist between cigarette smoking and bronchiogenic carcinoma apparently it is necessary that the man be a heavy smoker (at least a half pack of cigarettes per day) and that he has smoked for a long period of time (usually twenty years or more). (Fig. 1).

The commonly held belief that women smoke as much as men and that therefore they should show as great an incidence of bronchiogenic carcinoma as men is not borne out by a statistical study. In order to investigate this point two groups of hospital patients without lung cancer were interviewed. All of them were more than thirty years of age and they were comparable as regards economic status. One of these groups consisted of 552 women and the other of 780 men. Of the women it was found that 79.6 per cent were nonsmokers and only 1.2 per cent had smoked more than a pack of cigarettes a day for at least twenty years. By contrast this percentage of 1.2 is to be compared with one of 19.1 found in the males who did not have lung cancer. It is an interesting coincidence that this ratio of 19.1 to 1.2 compares closely with the sex ratio of incidence of bronchiogenic carcinoma, which was 18 males to 1 female in our last 150 cases. It is chiefly the girls and young women who are the female heavy smokers and they have not yet had time to smoke for twenty years or more. Perhaps in another decade or so there will appear a marked increase in the incidence of bronchiogenic carcinoma in the female. At present, and presumably during the time that the disease has been showing its great increase, it seems clear that men have been

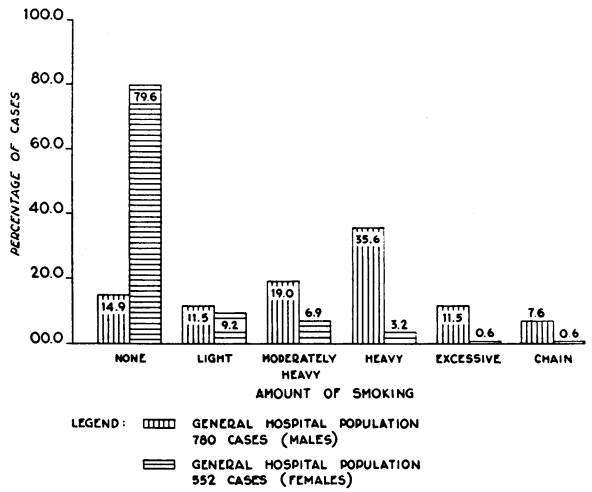

Fig. 2—Chart which shows the error in the belief that women in the cancer age (more than 40 years old) have smoked as much for as long (20 years) as men of the same age group. The designations "light", "moderately heavy", "heavy", "excessive" and "chain" have the same meanings as in Fig. 1.

much more exposed to the consequences of smoking than have women. Thus the greater preponderance of lung cancer in men may perhaps be explained (Fig. 2).

Of importance in considering a possible relationship between cigarette smoking and bronchiogenic carcinoma is the interesting article of Dungal,[20] the Professor of Pathology at the University of Iceland. He finds that in that country primary cancer of the lung is still a comparatively rare disease, being ninth in frequency among carcinomas of various organs. At the same time the amount of cigarette smoking is very much less than in other countries. For example, in 1932 the per capita consumption of cigarettes in Iceland was only one-eighth of that in the United Kingdom. Since World War II, however, the amount of cigarette smoking has greatly increased, but presumably an insufficient period of time has elapsed to have an effect on the incidence of bronchiogenic carcinoma.

The evidence, therefore, seems at least suggestive that excessive cigarette smoking carried out for a long period of time (twenty years or more) has been a factor in causing the remarkably increased frequency

of bronchiogenic carcinoma during the last thirty-five years. The proof is lacking and will remain absent until it becomes possible to produce cancer experimentally from some or all of the products contained in cigarette smoke. Various possibilities as to the source and nature of the carcinogenic substances come to mind. Of importance could be tars contained in the smoke and inhaled into the lungs, substances contained in the paper, such as arsensic, insecticides used in the growth of the tobacco, etc.

Another point brought out by the study of Wynder and the writer[19] is that if a man was an excessive smoker a few years ago the fact that he may have stopped smoking recently does not preclude the possibility that the smoking may still have been an important factor in the development of his recently acquired bronchiogenic carcinoma. This phenomenon is analogous to the lag which is well known to occur experimentally in the mouse between the application of a carcinogenic agent and the appearance of the tumor.

Of course, it is realized that excessive cigarette smoking is not the only etiological factor. After all in 2 per cent of our cases the patients had never smoked. Similarly it is well known that not every man who has been even a chain smoker for many years develops a primary cancer of a bronchus. There are no data available at present to indicate just what risk of developing such a cancer a man takes when he indulges in excessive smoking over a long period of time.

The common variety of bronchiogenic carcinoma, and the one which has shown the remarkable increase, is the epidermoid or squamous type. In many others the pathological diagnosis is "undifferentiated" type. Many histological varieties have been described by different pathologists. The most common designated types, other than those just mentioned, are the adenocarcinoma, the round cell and the oat cell carcinoma. There is considerable doubt, however, about the correctness of assuming that these so-called morphological differences noted in cell arrangements and types really represent different varieties of cancer. In many cases an examination of different parts of the same tumor will reveal morphological variations which could easily lead to different diagnoses if one should adhere too closely to rigid classifications. For example, if one recognizes a round cell or an oat cell carcinoma as a distinct type from an adenocarcinoma he may have difficulty in supporting his case if he will examine other parts of the same tumor. In general,

however, it seems to the writer that perhaps two common types occur, of which one is the epidermoid or squamous variety and the other the adenocarcinoma. Most of those tumors which are designated as undifferentiated seem to be less differentiated variants of the epidermoid type.

The importance of considering the morphological varieties here is that perhaps one can think of the epidermoid carcinoma of the bronchus as being a fundamentally different disease from the adenocarcinoma, at least in so far as its etiology and pathogenesis are concerned. At any rate that is a concept which the writer would like to suggest with the full realization of the danger of placing too much reliance on morphological classification. To some pathologists it may seem an error even to recognize the existence of adenocarcinoma of the bronchus. Yet unquestionably there are bronchial carcinomas which present microscopically an adenoid arrangement of the cells suggestive of an attempt to form glands. In our experience one finds such tumors about equally distributed between the two sexes and they are far less common than the epidermoid or squamous variety which is the ordinary tumor occurring predominantly in males.

According to the suggested concept one can think of the epidermoid or squamous carcinoma as being caused by a transmutation or metaplasia of adult bronchial epithelium due to the action of carcinogenic influences of which cigarette smoking seems to be an important one. On the other hand there is some evidence that the group of tumors, commonly called by various names such as bronchial adenoma, cylindroma, carcinoid, oat cell, round cell or adenocarcinoma in many instances may arise from fetal bronchial buds which have remained dormant until adult life. The evidence for this idea will be presented later. Here, however, it may be stated that if this concept is true those tumors just mentioned, which are either potentially or actually malignant, may be thought of as a conversion of embryonic epithelium rather than adult epithelium into cancer cells. This group of cancers then should be regarded as representing an entirely different condition from the ordinary common variety of epidermoid or squamous bronchiogenic carcinoma.

Fried[21] in 1934 proposed that the bronchial adenoma originates in the bronchial mucous glands. Previously Reisner[22] in 1928 and Wessler and Rabin[23] in 1932 had postulated more specifically that the origin was the epithelium of the ducts of the mucous glands. In 1941 Goldman and Stephens[24] considered that the tumor can come from the epithelium of

either the ducts or the glands. Stout[25] likewise in 1943 considered the bronchial glands to be the origin. In 1950, in an excellent review of the subject of adenomatous tumors of the bronchi, Goldman and Conner[26] propose that the epithelial cells of the serous and mucous glands of the trachea and bronchi, or the ducts of these glands, form the origin of the so-called bronchial adenomas, the cylindromas, the carcinoids, the so-called mixed tumors and the carcinomas which may arise from any of them. There is no good reason to doubt the correctness of any of these hypotheses. None of them really is opposed to the idea advanced by Womack and the writer[27] in 1938, that the so-called bronchial adenoma is derived from a fetal bronchial bud which has remained dormant. The only disagreement that can be said to exist is that according to our theory many of the varieties of tumor just mentioned arise in latent embryonic bronchial buds which contain the bronchial glands, whereas the authors just quoted apparently assume that the tumors arise from adult and fully formed glands and ducts. Harris,[28] after a study of human fetuses and newly borns, points out the similarity of infantile types of structures, especially the bronchial mucous glands and the peribronchial and peritracheal lymphadenoid tissue, to the histologic findings in bronchial adenoma. Since, in the material studied, the bronchial mucous glands occurred not only just beneath the mucosa but more deeply between the cartilaginous rings, and since the lymphadenoid tissue was found not only peribronchially and peritracheally but within the walls of bronchi and trachea as well, Harris states that it can be deduced that tumors arising from such tissues may be intramural or extramural or may extend into the bronchial or tracheal lumen. He also mentions the well-known fact that adenomatous tumors have been found in childhood and refers to the article by himself and Schattenberg[29] in which several such tumors in children, one only seven days old, were reported. Finally he states that his observations are compatible with the observations and ideas of Womack and the writer.[27]

One reason for regarding the group of tumors commonly designated as adenocarcinoma, as well as oat cell, round cell carcinoma, cylindroma and carcinoid as essentially a different condition from the epidermoid or squamous cancer of the bronchus is the fact that there is no convincing evidence that cigarette smoking has any etiological influence in the production of the former group of cancers. In fact when a bronchiogenic carcinoma occurs in a patient, male or female, who has never been a

smoker it is more likely to be one which is diagnosed as an adenocarcinoma or one of its variants (oat cell, round cell carcinoma, etc.) than as an epidermoid carcinoma. Moreover there is no evidence that the adenocarcinoma has participated in the striking increase in bronchiogenic carcinoma in general. Although apparently there are actually more cases of adenocarcinoma found than formerly, the small increase in this type, in contradistinction to the large number of cases of epidermoid carcinoma, can probably be accounted for by such factors as the greater number of people in the cancer age nowadays, better means of recognition, etc.

According to the concept mentioned above it seems tempting to assume that those carcinomas designated as adenocarcinoma, oat cell and round cell carcinoma arise from an embryonic bronchial bud which has failed to develop into normal tissue and has remained dormant for many years before being transformed into a carcinoma. The fact is of course well established that in the growth of the embryo the lungs are formed by a process of budding from the trachea which in turn is formed from the embryonic foregut.

In developing this concept the so-called bronchial adenoma furnished the first suggestion. Often the microscopic appearance of this tumor resembles fetal lung so closely that it is practically impossible to distinguish it from the lung of, for example, a 16 weeks old human embryo. So far as I know the first one to note this similarity was Bremer[30] of the Department of Anatomy at Harvard who reported it to Churchill.[31] For the most part the cells contain very little cytoplasm so that they give the appearance of consisting chiefly of nuclei. Moreover they are usually round or oat shaped.

The next point to establish was whether or not these so-called adenomas ever become malignant by developing into carcinomas. When in 1938 Womack and I[27] offered evidence that this tumor is potentially malignant as demonstrated by the invasion of neighboring lymph glands, we found no supporters of the idea. For example, in 1941 Foster-Carter[32] of the Brompton Hospital, London, from a study of twenty-two cases, stated that he had found no evidence of malignancy except perhaps slight invasion of the bronchial wall in a few instances. Strangely also in 1944 Engelbreth-Holm[33] of the University Institute of Pathological Anatomy of Copenhagen in an article which carried the title of "Benign Bronchial Adenomas" concluded that there was little evidence that those tumors

ever become malignant although in all of his twelve cases he reported there was marked invasive growth. Now, however, many cases of undoubted malignancy have been reported in which metastases were found at autopsy not only in the regional lymph glands but in the liver and other distant organs as well. (See, for example, Adams, Steiner and Bloch,[34] Anderson,[35] Stowell,[36] Bigger,[37] Alexander[38] and Chamberlain and Gordon[39].) In 1945 Womack and I,[40] in a paper presented to the American Association for Thoracic Surgery, reported two cases in which autopsy was performed after bronchoscopic biopsies had established the diagnosis of so-called adenoma. In both cases metastases were found in the liver. In one case the bronchoscopic biopsy had been made four years prior to the death of the patient. In the carcinomas which arise in the so-called adenomas the cellular structure corresponds closely with that of the latter tumors. In other words the prevailing type of cell is one which has very little cytoplasm and therefore seems to consist chiefly of nucleus. It has the morphological characteristics of the oat cell or round cell seen in those carcinomas which are designated by some pathologists by those names. Often also the cells are arranged in groups which are strongly suggestive of an adenoid structure and because of that arrangement many pathologists would use for the tumor the name of adenocarcinoma.

Criticism against the concept that the so-called adenoma and the carcinoma which is derived from it may represent an embryonic bronchial bud which has remained dormant without forming normal lung tissue has been made on the ground that if this conception is correct then one should expect often to find such buds during the routine examination of lungs. It should be understood, however, that they are of microscopic size unless they have become enlarged sufficiently to be recognized as tumors.

In 1904 Albrecht[41] coined the term "hamartoma" for a peculiar tumor of the liver. By this term he meant to imply that it was an expression of an abnormal growth of the normal structures of the organ. The word is derived from the Greek word, "hamartia," which means failure to reach the goal. The idea of Womack and the writer that some of the tumors of the bronchi and lungs result from the failure of embryonic bronchial buds to develop into normal adult structures is in line with Albrecht's conception of "hamartoma" concerning his tumor of the liver, and in our article of 1938[27] we called attention to the similarity

of our own conception of the origin of these tumors to that of Albrecht for the tumor of the liver described by him. Probably also of a similar nature are the carcinomas which we[42] reported arising in congenital cystic disease of the lung and in association with other developmental abnormalities of the lung. Although some of the recent writers have applied the term "hamartoma" to the tumors which seem to us to arise in fetal bronchial buds, most authors still designate them as bronchial adenomas. Perhaps it is fair enough to state that even the use of the term hamartoma implies that the tumor has arisen in an embryonic rest. Those who use that term therefore seem unconsciously to agree with our conception of its origin.

In our first article in 1938 Womack and I[27] noted a resemblance of these tumors to the mixed tumors of the salivary glands and therefore proposed the name of mixed tumors of the bronchus. The reason for this suggestion was that in some of the cases we found cartilage and even bone, and in some there was an adenoid arrangement of the epithelium like that often seen in the salivary gland tumors. Names, however, are of little importance.

Of passing interest is the possibility that some of the tumors of the bronchus, other than those of predominantly epithelial type, also may arise from embryonic buds. For example, a chondroma, a fibroma or a lipoma may have such an origin. The embryonic bud is composed not only of endoderm but of course of mesoderm as well. The latter is destined to form connective tissue, smooth muscle, bronchial cartilage, and any other tissue of mesoblastic origin. If, therefore, the mesoblastic tissue reacts abnormally to some unknown growth stimulus a tumor may arise in which mesoblastic tissue will predominate. The chondroma, fibroma and lipoma could perhaps be explained on that basis. Although those tumors are rare we have had several examples of each kind. Possibly a bit of additional evidence that such tumors arise from bronchial buds is the fact that epithelial elements have been reported in chondroma of the bronchus by McDonald, Harrington and Clagett,[43] a finding which we have confirmed in some of our own cases. Since the buds contain both endodermal and mesoblastic elements it might be expected that tumors arising from them would be composed of both elements. Just as the epithelial elements may give rise to a carcinoma, so malignant tumors may also arise from the mesoblastic components. Thus a fibrosarcoma may develop. Examples of that tumor have been reported recently by

Black[44] from our clinic, by Carswell and Kraeft[45] and by Curry and Fuchs.[46] Even more striking, however, is the occurrence of a combination of sarcoma and carcinoma in the same tumor. We have had two examples of the latter combination which will be reported by Bergman, Ackerman and Kemler.[47]

Although not arising in a bronchus there is another variety of primary carcinoma of the lung which should be mentioned briefly. It has been recognized only recently. It has been given various names of which the most commonly used are perhaps alveolar carcinoma, multiple adenomatosis and carcinoma mucocellulare. One of the most striking features of the condition is that it has a multiple origin. However, when the tumor is first recognized the multiple origins may all be confined to one lobe or one lung. The tumor arises in the parenchyma of the lung apparently in the cells lining the alveoli. The name "multiple adenomatosis" has been applied to the condition because sometimes one can recognize the multiple sites of origin as several nodules. The few cases which up to the present have been reported have either been uniformly fatal or apparently on the way to becoming so, with perhaps one exception. That exception is a case designated as a carcinoma mucocellulare and reported by Osserman and Neuhof.[48] After a lobectomy the patient was alive and well five years later. In three cases of my own one of the patients died within three years after lobectomy and another one slightly more than three years after a pneumonectomy. In the third case, although the patient is still living, less than a year has elapsed since a lobectomy was performed.

The condition is sometimes, but not always, characterized by the secretion of a large amount of mucus which may be coughed up by the patient and apparent also in the specimen of the tumor itself. Several case reports will be found in an article by Delarue and the writer.[49] Others will be found in articles by Drymalski, Thompson and Sweany,[50] by Wood and Pierson[51] by Stephens and Shipman,[52] by Swan,[53] and by Laipply and Fisher.[54]

A remarkable fact about this recently discovered tumor is that it seems to be identical in both gross and microscopic appearance, as well as its clinical course, to a disease of sheep known generally as "jagziekte." This name, a South African word, which means "driving sickness," has been applied to the condition because it was in South Africa that the disease was first recognized and carefully studied. It is now prevalent in

many parts of the world. In Iceland it occurs in epidemic form and is responsible for enormous losses of sheep. In recent years it has been recognized in the Western part of the United States. There seems to be rather general consent among pathologists who have studied this disease in the sheep that it is due to a virus which has not yet been found. Cowdry[55] was one of the pioneers in the investigation of the disease.

Summary

Bronchiogenic carcinoma has shown an amazingly increased incidence within the last thirty-five years and the increase seems to be progressive.

At the present time it is overwhelmingly a male disorder.

More and more evidence has been accumulated that excessive cigarette smoking is an important etiologic factor, although not the only one.

The great preponderance of the disease in the male sex is not due to any special immunity of females. Rather it seems due to the fact that, contrary to popular belief, many fewer women of the cancer age smoke than do men. A statistical study of this question demonstrates the truth of this statement.

The marked increase in bronchiogenic carcinoma has been in the type usually designated as epidermoid or squamous, or a variant recognized as a undifferentiated type.

A corresponding increase has not been noted in the adenocarcinoma or in those types which some pathologists call round cell or oat cell carcinoma.

Evidence is presented which seems to indicate that epidermoid carcinoma of the bronchus presents an entirely different etiology from that of adenocarcinoma, oat cell or round cell carcinoma. The suggestion is made that the former type of cancer is due to the metaplasia of adult to carcinomatous epithelium under the influence of one or more carcinogenic agents but that the adenocarcinoma, including the oat cell and round cell carcinoma, arises in a latent embryonic bronchial bud.

The recently recognized alveolar carcinoma, sometimes called multiple adenomatosis, which closely resembles the disease of sheep known as "jagziekte," is briefly discussed.

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